Rehabilitation in Oncology
Vol. 7, No. 2, 1989

Function of the Lymphatic System

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The lymphatic system is essentially a drainage system within the human body. It consists of a large network of vessels called *lymphatics,* and *lymph* is the fluid which flows into the lymphatics. Lymph originates from the plasma as the difference between the filtration and absorption of fluid across the capillary. The compostion of lymph is almost identical to that of the tissue fluid in the part of the body from which the lymph is derived. Tissue fluid from the liver and intestines is the source of more than half of all lymph.

Three main functions are served by the lymphatic system. First, it is responsible for the return of proteins from the interstitial fluid. Proteins become concentrated in the interstitial fluid before it flows into the lymphatics because almost none of the protein that leaks into the tissue spaces from the arterial ends of the capillaries can be absorbed at the venous ends of the capillaries. On the other hand, most of the water leaking out is reabsorbed. As a result, whereas fluid filtering from the arterial ends of the capillaries has a protein concentration of less than 0.2 percent, the interstitial fluid has a protein concentration of some ten times this value. As protein accumulates in the interstitial fluid, this accumulation increases the tissue colloid osmotic pressure. This increased osmotic pressure slows capillary reabsorption at the venous end and, as a result, tissue fluid volume and thusly interstitial fluid pressure increases. Interstitial fluid is then forced into the lymphatic capillaries by this increased pressure, and the excess accumulation of proteins is carried along with the fluid. Protein concentration is thereby kept at a low level by this continual "wash-out" process. This function of the lymphatics is highly important because no other route exists except the lymphatics for return of excess proteins to the circulatory system. A second function of the lymphatic system is the removal and destruction of bacteria and other large particles. These are able to enter into the lymph system by pushing between the endothelial cells of the lymphatic capillaries. The lymph carries such debris to the lymph nodes, where it is removed and destroyed. Lastly, the lymphatic system provides the pathway by which fat absorbed from the GI tract reaches the blood.

Anatomy of the Lymphatic System

Lymph is returned to the general circulatory system via one of the two lymph drainage pathways. The lymph from the entire lower half of the body and the left half of the upper body ultimately flows into a large lymphatic trunk called the *thoracic duct.* The *right lymphatic duct* collects lymph from the right upper extremity and the right side of the head, neck and thorax. Lymph from these main ducts empties into the venous system at the juncture of the internal jugular and subclavian veins on their respective side.

In comparison with the total exchange of fluid between the plasma and the interstitial fluid, the amount of lymph flow is relatively small. Most of the fluid filtering from the arterial capillaries flows among the cells and is finally reabsorbed back into the venous capillaries. On the average, about one-tenth of the fluid enters the lymphatic capillaries and returns to the blood via the lymphatic system instead.

The lymphatic system begins as a network of blind-end *lymphatic capillaries* (terminal lymphatics) which permeate most tissues of the body. Unlike the larger lymphatics and collecting ducts, the terminal lymphatics are composed of a single layer of endothelial cells. When interstitial fluid pressure exceeds that in the terminal lymphatics, the interendothelial junctions are opened; when the interstitial fluid pressure is less than that in the terminal lymphastics, they close. In most tissues, these overlapping interendothelial cellular junctions act as valves and allow unidirectional flow of interstitial fluid into the lumen of the terminal lymphatic. Via bulk flow fluid, macromolecules and other substances pass into the terminal lymphatics through the interendothelial junctions. Under normal conditions, only a small fraction of the endothelial junctions are open. As the interstitial fluid pressure begins to increase, more of these junctions will open up. The terminal lymphatics do not collapse when there is increased interstitial fluid volume because of support from *anchoring filaments.* These are structures which are attached to the lymphatic capillary walls on one end and to the connective tissue between the surrounding cells on the other end. As interstitial fluid volume increases, it produces

a pulling force on the anchoring filaments. This pulling force is thereby transferred to the lymphatic capillaries, preventing their collapse.

Lymphatic capillaries join to form a series of collecting vessels of increasing size as they course centrally from the periphery. The lymphatic vessels, or *lymphatics,* run in close relationship to the venous system. Although thinner walled than veins, lymphatics are similar to them in tissue structure and in that they, too, possess valves.

Lymph nodes are interposed at irregular intervals along the lymphatics. They range in size from one millimeter to one centimeter in diameter and number between 500 to 1,000 in the average adult. Their function is to filter the lymph of foreign particles and to produce lymphocytes which neutralize toxins.

Interestingly, and perhaps not what one might expect, the interstitial fluid is not in a freely mobile state but is held in a gel that fills the spaces between the cells. Large quantities of mucopolysaccharides are contained within the gel. Diffusion of small molecules through the gel occurs almost as effectively as it does through free fluid. However, the fluid in the gel is not easily moved from one tissue part to another but is rather, for the most part, held in place by the gel. When edema occurs, the gel can imbibe a small quantity of the edema fluid to swell some 30 to 50 percent. With continued increase in fluid volume, all of the additional fluid that collects will remain in a free state, highly mobile through the interstitial spaces. In this condition, *pitting edema* will occur, as fluid moves freely to another area from the site where pressure has been applied. *Dependent edema* occurs as the pull of gravity draws this free fluid downward.

Rate of Lymph Flow

The rate of lymph flow is determined by two main factors: 1) the lymphatic pump, which is controlled by intrinsic and extrinsic forces, and 2) the interstitial fluid pressure.

Lymph vessels can be compressed either by intrinsic contraction of the lymphatic walls themselves or by extrinsic pressure upon them from surrounding structures. Everytime the lymph vessel is compressed by pressure from any source, lymph tends to be squeezed in both directions but because the valves open only in the central direction, the fluid moves unidirectionally.

A *lymphangion* defines the segment between two adjacent valves, and it is the basic functional unit of the lymphatic system; each single unit contracts as a whole. The contractions are initiated by the stimulus of radial distention (transmural vessel distention) of the lymphangion. Each vessel segment has a characteristic threshold value that the stretch must attain in order to stimulate a contraction, and each contraction is followed by a period of relaxation. This contractile activity is of smooth muscle myogenic origin. It usually begins at the most distal lymphangion and spreads centrally from one unit to the next towards the emptying ducts. As in the Frank-Starling law of the heart wherein the end diastolic stretch increases the strength of the next contraction, the intensity of a lymphangion contraction depends largely on the amount of preload distention present in the wall just before the onset of the contraction. Frequency and amplitude of contractions increase with increasing initial vessel distention up to a certain point and after that point is reached, decrease despite further increase in the preload.

The lymphatic smooth muscle contractions can also be modulated by a number of humeral mediators such as histmine, adrenaline, seratonin, prostaglandins, dopamine, acetylcholine, ATP and ADP. Intramural nerves of the lymphatics present an additional mechanism for the control of lymph propulsion, via an adrenergic response.

The rhythmic movements of organs and movements of muscles exert an extrinsic pressure on the lymphatic vessel walls. Lymph flow in the heart, lungs and intestines is influenced passively by arterial pulsations, respiratory rhythm and gut motility. In the peripheral lymphatics, the pressure caused by skeletal muscle action (specifically, rhythmic rising onto toes) on the lymphatics in normal volunteers was less than 0.2mm Hg or five percent of the pulse amplitude produced by the intrinsic contractions of the lymphatics, and the muscle action caused only a slight rise in pulse frequency. This was consistent with the finding that approximately one-tenth of the intrapleural pressure is transmitted to the tissues of the lower mediastinum. Thus, investigators have proven that, in contrast to what had been believed up until the last decade, it is not so much the continued massaging effects of skeletal muscles and respiratory movements which propulse lymph flow in humans but, rather, intrinsic contractions of the lymphatics themselves.

The other major determinant of the lymph flow rate is the interstitial fluid pressure. Any factor that tends to increase interstitial fluid increases the rate of lymph flow. These factors include: 1) elevated capillary pressure, 2) decreased plasma colloid osmotic pressure, 3) increased permeability of the capillaries, and 4) increased interstitial fluid protein.

Pathophysiology and Etiology of Edema

Pathology of the lymphatic system can produce edema by way of the following:

1) Increased capillary pressure - an abnormally high mean capillary pressure forces more fluid to flow out of the capillary than returns into the capillary. As a result, excess fluid collects in the tissue spaces. Any clinical condition which causes venous obstruction or arteriolar dilatation can produce such an effect, i.e., deep vein thrombosis blocks return of the blood from the affected area to the heart, thereby causing back-pressure on capillaries and edema in the involved tissues. Obstruction of venous return due to cardiac failure causes blood to dam up in the venous system with resultant systemically increased capillary pressure. An allergic reaction such as hives causes arteriolar dilatation and increased capillary pressure. Kidney fluid retention will eventually in-

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crease capillary pressure due to the increased total amount of extracellular fluid.

2) Decreased plasma proteins - when the colloid osmotic pressure of the plasma becomes much lower than is normal, the capillary fluid pressure will be left far outweighing it, which will promote the tendency for fluid to leave the capillaries and diffuse into the tissue spaces. The interstitial fluid pressure will then rise. Extensive burns will cause loss of large quantities of albumin from the plasma and thus result in edema throughout the whole body because of lowered plasma colloid osmotic pressure. Nutritional edema occurs in persons who lack sufficient protein in their diets and therefore cannot form adequate quantities of plasma protein.

3) Increased permeability of the capillaries - when capillary permeability is increased, protein molecules may begin to pass from the plasma into the interstitial spaces with ease. The increased tissue colloid osmotic pressure draws more fluid into the tissue spaces and in turn leads to progressive edema. This occurs clinically in burns, which overheat capillaries and make them friable; their pores enlarge and become more permeable.

4) Lymphatic obstruction - obstruction of the lymphatics may occur due to removal of lymph node groups, as in axillary or groin node dissection. Ionizing radiation can cause tissue necrosis and fibrosis and lead to obstruction of lymph vessels. When lymph flow is blocked, this will cause increasing amounts of protein to collect in the interstitial spaces, as protein will continue to diffuse out of the capillaries but have no where else to go since it is blocked from the lymph system and is unable to be reabsorbed by the blood capillary system. The concentration of tissue protein may then near the concentration of the plasma protein, which is normally the much higher of the two. Interstitial fluids must rise dramatically to balance the tissue colloid osmotic pressure. Such elevated tissue pressure rapidly expands the tissue spaces and results in severe edema. Lymphatic hypertension will ensue distal to the blockage and lead to dilation of lymph vessels and valve incompetency. The protein rich environment allows bacteria to thrive in the area of lymphedema. Resultant infection often leads to thrombosis of lymph vessels and further blockage. Prolonged lymph stasis can lead to fibroblastic proliferation, progressive interstial fibrosis in the associated tissues, and obliteration of additional lymph vessels. After prolonged obstruction, lymph vessels lose their ability to contract intrinsically. Alternatively, either peripheral lymphatico-venous communications or collateral lymphatic circulation may develop to mitigate the problem. Also, lymphatic regeneration may occur following ligation of the lymphatics, as lymphatics possess strong regenerative ability. The opening of newborn lymphatics can actually reduce the load of blocked lymphatics. Scars, however, can prevent regeneration of lymphatics.

The primary lymphatico-venous communication is formed by the junction of the thoracic duct at the left subclavian vein and internal jugular vein. Under normal conditions, this junction is always functional. When lymphatic occlusion occurs, a number of secondary lymphatico-venous communications may become functional. Increased lymph pressure (lymph hypertension) opens lymphatico-venous communications distal to the occlusion point. The valves at these lymphatico-venous junctions may offer high resistance. However, the pressure gradient during lymphatic hypertension can become large enough to overcome the resistance and allow sufficient lymph flow into the venous system. It is not known if these lymphatico-venous communications exist throughout life or if they develop only after prolonged hypertension. If these communications do not develop within an appropriate period of time, pathological conditions take place within the lymphatic vessel wall, and the lymph vessels lose their ability to contract intrinsically.

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